

REMARKS

Claims 1-7 are all the claims pending in the application.

I. RESPONSE TO REJECTION UNDER 35 U.S.C. § 103

Referring to pages 2 and 3 of the Office Action, Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of U.S. Patent No. 6,506,747 ("Betageri") and U.S. Patent No. 6,958,339 ("Kubota") in view of Haleblian et al. (J of Pharmaceutical Sciences, (1969), 58, pp 911-929), Chemical & Engineering News, Feb. 2003, Brittain et al. (Polymorphism in Pharmaceutical Solids, pages 1-2, 185), U.S. Pharmacopeia, 1995, pp 1843-1844, Muzaffar et al. (J. of Pharmacy (Lahore) 1979, 1(1), 59-66), Jain et al. (Indian Drugs, 1986, 23 (6), Taday et al. (J of Pharm. Sci, 92 (4), April 2003, 831-838) and Concise Encyclopedia Chemistry, page 872-873 (1993).

Applicants respectfully traverse. The combination of applied art does not render obvious the subject matter of the present claims.

Claim 1 is directed to a crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide. As acknowledged by the Office Action, the subject matter of Claim 1 is novel (not anticipated under 35 U.S.C. § 102). Indeed, Applicants emphasize that the characteristics and physical data of a crystal of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinilide are not at all disclosed in the applied art. For the following reasons, the subject matter of Claim 1 (and all dependent claims) is also not taught or suggested (rendered obvious under 35 U.S.C. § 103) by the combination of applied art.

As an initial matter, Applicants point out that the primary references, Betageri and Kubota, are Patent References 3 and 1, respectively, mentioned at pages 1-4 of the specification.

Secondary to Betageri and Kubota, the examiner has cited many references generally describing the possibility of the existence of a polymorphic crystal. However, these references merely generally suggest that polymorphism may possibly exist when there is a crystal. For example, the Haleblian document shows a percentage in which polymorphism was found at

Table 1 on page 912. The examiner's position thus seems to be that, because steroids may easily crystallize and cases of polymorphism are known for steroids, one skilled in the art may consider the existence of polymorphism for a new steroid compound.

Applicants respectfully disagree that any of these references, whether considered alone or in combinations of two or more, lead to a conclusion of obviousness under 35 U.S.C. § 103 for the presently claimed subject matter.

It is understood in the field of chemistry that crystallinity is different, even between position isomers, and that crystallinity differs when a hydrogen atom of a compound is changed to a methyl group. Accordingly, even if Kubota and Betageri are taken into consideration, no reasonable expectation has been established on the present record as to whether the specifically claimed compound crystallizes or not. It is not described in the references as to whether the compounds disclosed in the references easily crystallize or not and whether polymorphism exists.

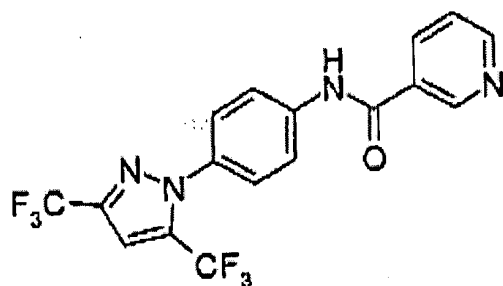
Importantly, the examiner describes polymorphism as "highly unpredictable" at page 4 of the Office Action.

The references U.S. Pharmacopeia etc. teach that "only one crystalline form is thermodynamically stable." However, each of the α (see, *e.g.*, present Claims 2 and 5) and β (see, *e.g.*, present Claims 3 and 6) crystals of the presently claimed nicotinilide is stable (stable enough to be used as a raw material for producing a pharmaceutical product). Whether a certain specific polymorphic crystal exists stably can be found only after obtaining the crystal. It is not foreseen at all beforehand.

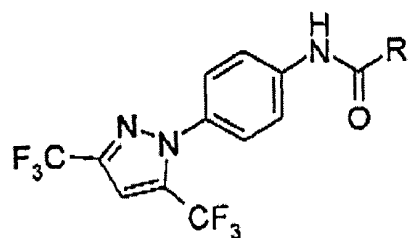
In short, at least the following steps would be required to reach the presently claimed subject matter from Kubota, Betageri, etc.: (1) selecting the specifically claimed compound; (2) crystallizing the specific compound; (3) determining the existence of polymorphism; and (4) confirming the stability of the crystal. Thus, for the reasons discussed above, the only manner of reaching the presently claimed subject matter from the combination of applied art would be through the use of impermissible hindsight reasoning.

In addition, Applicants provide below further explanation as to why the combination of applied art fails to provide a reasonable expectation that the presently claimed compound can crystallize.

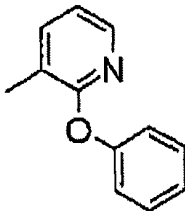
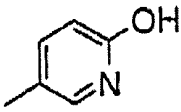
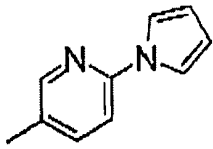
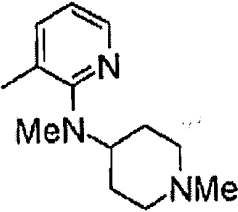
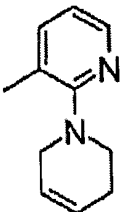
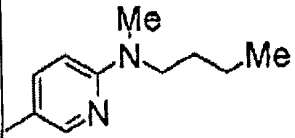
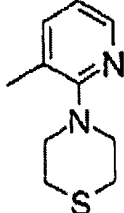
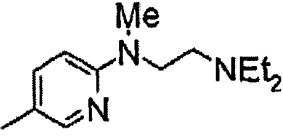
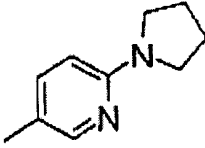
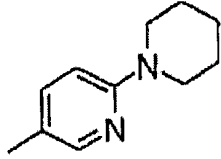
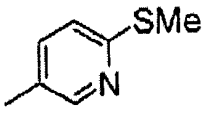
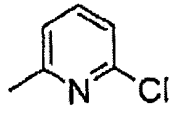
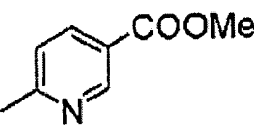
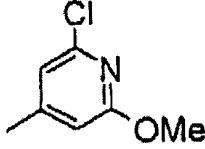
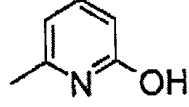
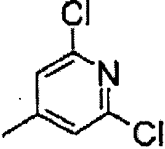
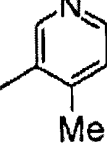
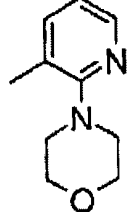
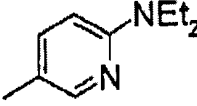
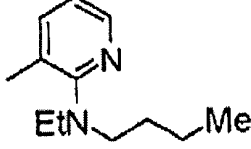
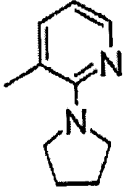
With respect to a nicotinamide derivative, Kubota discloses the following compound (Ex. 36):

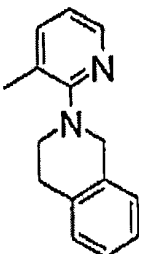
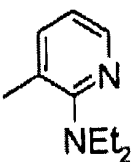
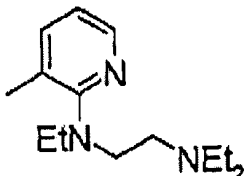
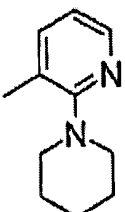
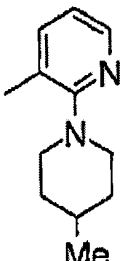
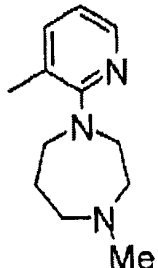
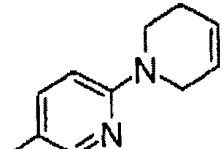
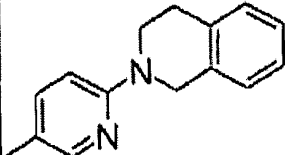
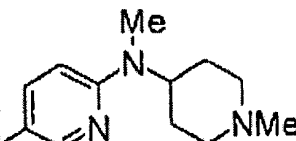
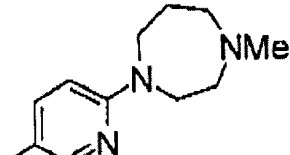
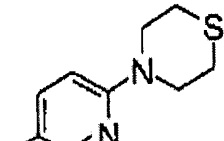
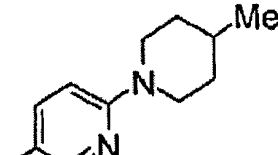


Also, JP 2000-256358 ("JP '358"), which is already of record, and for which Applicants are submitting a machine-generated translation concurrently herewith in an Information Disclosure Statement, discloses the following compounds.



| Ex | R | Ex | R | Ex | R |
|----|---|----|---|----|---|
| 5 | | 6 | | 10 | |
| 11 | | 14 | | 15 | |
| 16 | | 18 | | 20 | |
| 28 | | 41 | | 46 | |

| | | | | | |
|-----|---|-----|---|-----|---|
| 62 |  | 64 |  | 69 |  |
| 76 |  | 77 |  | 78 |  |
| 79 |  | 80 |  | 81 |  |
| 82 |  | 89 |  | 91 |  |
| 97 |  | 100 |  | 106 |  |
| 109 |  | 112 |  | 113 |  |
| 114 |  | 115 |  | 116 |  |

| | | | | | |
|-----|---|-----|---|-----|---|
| 117 |  | 121 |  | 122 |  |
| 123 |  | 124 |  | 125 |  |
| 128 |  | 129 |  | 130 |  |
| 131 |  | 132 |  | 133 |  |

Among these compounds, only the compounds of Examples 5 and 6 of JP '358 are disclosed in the specification as crystals. Even if, for the sake of argument, one assumes that the compounds having a description about melting point in the physicochemical data (Dat) are assumed to be crystals, there are only seven compounds in total (Example 36 of Kubota and Examples 5-6, 14-16, and 20 of JP '358). Except Ex. 36 of Kubota, these compounds are limited to (i) hydrochloride (Ex. 5 of JP '358) or (ii) compounds having a substituent with a large atomic weight (*e.g.*, S, Cl, and Br) (Examples 6, 14, 15, 16 and 20 of JP '358). In this regard, although Examples 18, 41, 79, 89, 91, 100, 109 and 132 of JP '358 are described as having S or Cl atoms, it is not described that these compounds were obtained as crystals. Moreover, it is not described

at all as to whether there are other polymorphic crystals, and whether these different types of polymorphic crystals can be separated by crystallization. Still further, Applicants emphasize that the compounds of Examples 28 and 112 of JP '358 have a methyl group as a substituent, but these compounds are not described as crystals.

For all of the foregoing reasons, the presently claimed crystal is not obvious, even when the combination of applied art is fully taken into consideration. Withdrawal of the present §103 rejection is requested.

II. RESPONSE TO REJECTION UNDER 35 U.S.C. § 112

Referring to pages 4-7 of the Office Action, Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Applicants respectfully traverse. The subject matter of Claim 7 satisfies each and every requirement of 35 U.S.C. § 112.

As an initial matter, the present rejection is unclear. The rejection is first identified as a §112, first paragraph, written description rejection. Through the first full paragraph at page 5 of the Office Action, the rejection is discussed in terms of “lack of description.” Then, at the second full paragraph on page 5 of the Office Action, the Forman factors for evaluating enablement are listed. The remainder of the remarks running through page 7 are an evaluation of the Forman factors, and it is concluded that “it is not seen where [Claim 7] is enabled by the instant application.”

Regardless of whether it was intended for the §112 rejection of Claim 7 to be a written description or an enablement rejection, Applicants state that the rejection is without merit. Contrary to the assertion in the Office Action, the pharmaceutical composition of Claim 7 is not limited to a specific polymorphic form.

Claim 7 depends from Claim 1 and is directed to a solid pharmaceutical composition. The composition of Claim 7 comprises the crystal according to Claim 1 and a pharmaceutically

acceptable carrier. The crystal of Claim 1 is 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide.

Unlike the embodiments of dependent Claims 2 and 5, which are directed to the α -type polymorphic crystal (see page 5, line 25, through page 6, line 8), and the embodiments of dependent Claims 3 and 6, which are directed to the β -type polymorphic crystal (see page 6, lines 1-8), the crystal of Claim 1 is not limited to any particular polymorphic type. Thus, the solid pharmaceutical composition of Claim 7 is also not limited to a specific polymorphic type. Instead, as stated at the top of page 5 of the specification, the present inventors found that any of the polymorphic crystals of 4,6-dimethyl-4'-[3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl]nicotinamide are preferable as a raw material for producing pharmaceutical compositions. In this regard, Applicants direct the examiner's attention to page 6, lines 9-15, and Example 1 of the specification.

Further, the solid pharmaceutical composition of Claim 7, which is not limited to a specific polymorphic type, is more than adequately described in the present specification and is enabled by, for example, the descriptions in the specification identified above.

For example, the examiner seems to believe that the polymorphic crystals are not stable and can change into different forms, therefore, there is no enablement for one skilled in the art. However, Applicants describe at page 6 of the specification that:

Because both the α type and β type crystals are stable at 5 to 60 °C for at least three months and can be highly purified by recrystallization, these crystals may be used as raw materials for producing pharmaceutical products.

In addition, Table 1 on the same page indicates the stability.

From these descriptions, it is apparent to one of ordinary skill in the art that the pharmaceutical composition of Claim 7 may be prepared. Even assuming for the sake of argument that the form of the crystal changes, the rejection would remain unfounded because Claim 7 does not limit the form of the crystal to a specific polymorphic form.

In view of the above, withdrawal of the present §112 rejection is requested.

III. RESPONSE TO DOUBLE PATENTING REJECTION

Referring to page 8 of the Office Action, Claims 1-7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-8 of Kubota in view of Haleblian, Brittain, Chemical & Engineering News, Muzaffar, Jain, Taday, and Concise Encyclopedia Chemistry.

Applicants respectfully traverse.

The invention defined in present Claims 1-7 is not an obvious variation of the invention defined in Claims 1-8 of Kubota in view of Haleblian, Brittain, Chemical & Engineering News, Muzaffar, Jain, Taday, and Concise Encyclopedia Chemistry, for the same reasons as noted at Section I above. Touching on a few of the main points identified at Section I above, no reasonable expectation has been established on the present record as to whether the specifically claimed compound crystallizes or not. It is not described in the references as to whether the compounds disclosed in the references easily crystallize or not and whether polymorphism exists. Importantly, it is acknowledged at page 4 of the Office Action that polymorphism is "highly unpredictable." Whether a certain specific polymorphic crystal exists stably can be found only after obtaining the crystal. It is not foreseen at all beforehand.

In view of the above, withdrawal of the present double patenting rejection is requested.

IV. CONCLUSION

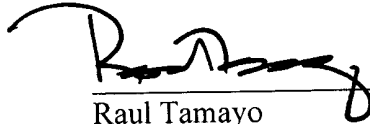
Reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

RESPONSE UNDER 37 C.F.R. § 1.111
U.S. Application No. 10/525,709

Atty. Docket No. Q86272

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: January 22, 2007